REMARKS

Claims 23, 25, and 27-29 are pending in the instant application. Claims 23, 25, and 27-29 have been rejected. Claim 23 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection Under 35 U.S.C. §102

Claims 23, 25, 27 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by Senter *et al.* ((1996) *Cancer Res.* 56:1471-1474).

Senter *et al.* teach methods of increasing the activation of prodrugs Paclitaxel and camptothecin (CPT-11) to active drugs in human and mouse tumor cells by the administration of rat serum carboxylesterase following administration of the prodrug.

The Examiner suggests that while the method by which the carboxylesterase protein of Senter *et al.* is prepared is different from that recited in claim 23, the isolation method does not affect the structure of the product produced and thus the protein of Senter *et al.* meets the limitations of the claimed method.

Applicants respectfully traverse this rejection.

In an effort to advance the prosecution of this application, Applicants have amended claim 23 to recite that the carboxylesterase used in activation of a prodrug is a rabbit carboxylesterase comprising SEQ ID NO:21 as taught throughout the instant specification. In contrast, the carboxylesterase taught by Senter *et al.* is isolated from rat. Accordingly, as the reference of Senter *et al.* does not teach each and every element

of the claimed invention as set forth by MPEP 2131, it does not anticipate it. It is therefore respectfully requested that this rejection be withdrawn.

II. Rejection Under 35 U.S.C. §103

Claims 23, 25, 27 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Senter *et al.* in view of Alexson *et al.* ((1994) *J. Biol. Chem.* 260:17118-17124). Claim 29 is also rejected under 35 U.S.C. §103(a) as being unpatentable over Senter *et al.* taken alone or in combination with Alexson *et al.*

The teachings of Senter *et al.* are discussed *supra*.

Alexson *et al.* teach the production of the rat serum carboxylesterase used by Senter *et al.*

The Examiner suggests that it would have been obvious to one of ordinary skill in the art to use the recombinant rat serum carboxylesterase in the method of Senter *et al.* as the recombinant enzyme could be obtained in much larger quantities as described in Alexson *et al.*

Further, the Examiner suggests that while Senter *et al.* and Alexson *et al.* do not teach the administration of rat serum carboxylesterase prior to administration of the prodrug, Senter *et al.* does suggest using rat serum carboxylesterase for cancer treatment and specifically states that "it may be possible to use rat serum carboxylesterase for prodrug activation *in vivo* by targeting the enzyme to tumors with an appropriate monoclonal antibody and then administering a prodrug such as PC or CPT-11" thereby suggesting the administration of the rat serum carboxylesterase prior to the administration of the prodrug. The

Examiner further suggests that one of skill in the art would have been motivated to administer the carboxylesterase first in order for it to be targeted to the tumor prior to prodrug administration as this would minimize side effects due to activation of the prodrug in non-tumor cells.

Applicants respectfully traverse this rejection.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed *supra*, Applicants have amended claim 23 to recite that the carboxylesterase used in activation of a prodrug is a rabbit carboxylesterase. While Senter et *al.* teaches the use of rat carboxylesterase for increasing the activation of prodrugs Paclitaxel and camptothecin, neither Senter et *al.* nor Alexson et *al.* teach or suggest that a carboxylesterase isolated from rabbit will be useful in promoting the cleavage of an ester or carbamate linkage of a prodrug to form an active drug in a cell or organism. Further, it would not be obvious to one of skill in the art that any carboxylesterase has the ability to promote the cleavage of a prodrug to an active drug as, for example, the

human carboxylesterase is inefficient at said conversion (see page 13, lines 9-22 of the instant specification) and shares a high degree of homology (83% similarity) with the rat serum carboxylesterase of Senter *et al.* (see page 1474, first column, lines 6-8). Thus, there would be no reasonable expectation of successfully substituting the rat carboxylesterase of Senter *et al.* and Alexson *et al.* with a rabbit carboxylesterase to arrive at the claimed invention.

Applicants respectfully disagree with the Examiners suggestion that claim 29 is obvious in view of Senter *et al.* taken alone or in combination with Alexson *et al.* As indicated *supra*, Senter *et al.* and Alexson *et al.* fail to teach, suggest, or motivate the skilled artisan to combine the teachings of the cited references to arrive at the inventive method set forth in amended independent claim 23. As set forth by both the Court of Appeals for the Federal Circuit and the MPEP, when an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and MPEP § 2143.03. Accordingly, the cited combinations of prior art references can not render obvious claim 29. Withdrawal of these rejections is therefore respectfully requested.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

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Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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